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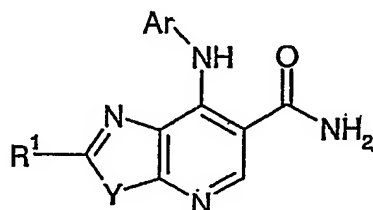
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(54) Title: IMIDAZO AND THIAZOLOPYRIDINES AS JAK3 KINASE INHIBITORS



(I)

(57) Abstract: The present invention relates to novel imidazo and thiazolopyridine compounds which are kinase inhibitors, methods for their preparation intermediates and pharmaceutical compositions comprising them. Formula (I)

NOVEL COMPOUNDS

The present invention relates to novel imidazo and thiazolopyridine compounds which are JAK3 Kinase inhibitors, methods for their preparation, intermediates and pharmaceutical compositions comprising them.

Janus Kinase 3 (JAK3) is a member of the Janus family of protein kinases. Although the other members of this family are expressed by essentially all tissues, JAK3 expression is limited to hematopoietic cells. This is consistent with its essential role in signaling through the receptors for IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 by non-covalent association of JAK3 with the gamma chain common to these multichain receptors. These cytokines all have a shared function in that they are involved in lymphocyte differentiation and proliferation. XSCID patient populations have been identified with severely reduced levels of JAK3 protein or with genetic defects to the common gamma chain, suggesting that immunosuppression should result from blocking signaling through the JAK3 pathway. Animal studies have suggested that JAK3 not only play a critical role in B- and T-lymphocyte maturation, but that JAK3 is constitutively required to maintain T-cell function. Modulation of immune activity through this novel mechanism can prove useful in the treatment of T-cell proliferative disorders such as transplant rejection and autoimmune diseases.

The role of JAK3 in mast cells has been described in knockout mice. Thus, IgE/antigen induced degranulation and mediator release were substantially reduced in mast cells generated from JAK3 deficient mice. JAK3 deficiency does not affect mast cell proliferation in vitro, it has also been shown that IgE receptor levels and mediator contents are identical in JAK3^{-/-} and JAK3^{+/+} mast cells. Therefore, JAK3 appears essential for the complete response of IgE challenged mast cells. The role of JAK3 in mast cell activation has been well established in murine system, however, there is no published data on mast cell function in the AR-SCID patients. Targeting JAK3 provides the basis for new and effective treatment of mast cell mediated allergic reactions.

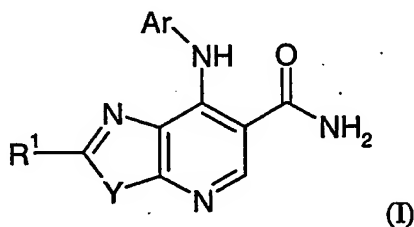
To date a number of JAK3 inhibitors has been disclosed, among them are quinazolines (Sudbeck, E. A. et al. Clinical Cancer Res. 5(1999)1569-82, WO 00/0202) and pyrrolo[2,3-d]pyrimidines (Blumenkopf, T. A. et al. WO 99/65909).

In the current application compounds, 4-anilinoquinoline-3-carboxamides, are claimed as JAK3 inhibitors. Structurally related compounds have previously been described as kinase inhibitors e.g. WO 00/18761 and WO 98/43960 disclose substituted quinoline-3-

carbonitrile derivatives. In a recent publication (Boschelli, D.H. et al. J. Med. Chem. 44(2001)822-33) one compound of the present invention has proved not to have any inhibitory capacity towards the activity of the protein tyrosine kinase Src. JAK3 is not mentioned in any of the above literature examples.

WO 02/092571 discloses a series of quinoline derivatives for use in the treatment of a disease mediated by JAK3.

There is a need for further compounds having this activity, and therefore the present invention provides a compound of formula (I):



wherein:

Y is NH, S or O;

R¹ is phenyl or a 5- to 7-membered heteroaromatic ring containing 1 to 3 heteroatoms, each of which is optionally substituted by one or more groups selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, S(O)_nC₁-C₈ alkyl or a group -R²-(CH₂)_p-R³;

n is 0, 1 or 2;

R² is a bond, NH, NC₁-C₈ alkyl, S or O;

p is 0 - 3;

R³ is NR⁴R⁵ where R⁴ and R⁵ are independently hydrogen or C₁-C₈ alkyl, or R³ is a phenyl ring, a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, or a 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, each of which can optionally substituted by one or more groups selected from CONR⁴R⁵, NR⁴R⁵, C₁-C₈ alkyl, C₁-C₈ alkoxy, S(O)_nC₁-C₈ alkyl, hydroxyl, CN, halogen,

NHCOC₁₋₈alkyl, R²-(CH₂)_p-OH or morpholine;

n is 1 to 4;

- 5 Ar is phenyl which can be optionally substituted by one or more groups selected from halogen, hydroxy, cyano, C₁₋₈ alkyl (itself optionally substituted by one or more hydroxy or cyano groups or fluorine atoms), CH₂-R⁶; CH₂O(CH₂)_nOC₁₋₆ alkyl, C₁₋₈ alkyl-NR³-R⁴, or a C₂₋₆ alkyl chain optionally containing an NR⁷ group in the chain and optionally substituted by one or more OH groups and optionally terminating in a cycloalkyl or phenyl
10 group, the cycloalkyl and phenyl groups themselves being optionally substituted by one or more hydroxyl groups;

- R⁶ is a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, an aryl or 5- to 7-membered heteroaryl group containing 1 to
15 3 heteroatoms selected from nitrogen oxygen and sulphur, each of which can optionally substituted by one or more substituents selected from hydroxyl or hydroxymethyl;

R⁷ is hydrogen or C₁₋₆ alkyl;

- 20 and pharmaceutically acceptable salts thereof.

- The term alkyl, whether used alone or as part of another group such as alkoxy, means any straight or branched chained alkyl group. The term aryl includes phenyl and naphthyl groups. Compounds of the present invention include all stereoisomers, pure and mixed
25 racemates, and mixtures thereof. Tautomers of compounds of formula (I) also form an aspect of the invention.

Preferably Y is NH or S.

- 30 Preferably R¹ is by SCH₃, SOCH₃, O-Ph-CONH₂, O(CH₂)₃-N(CH₃)NH(CH₂)₃-morpholine, O(CH₂)₂-morpholine, OCH₃, O(CH₂)₂-N(CH₃)₂, 2-(3-aminophenoxy), 4-methoxyphenoxy, or pyridyl or phenyl optionally substituted by OH, N(CH₃)₂, OCH₃, CN, fluoro, chloro, S(O)₂CH₃, NHCOCH₃, O(CH₂)₂OH, N(CH₃)(CH₂)₂OH, morpholine or O(CH₂)₂-OH

- 35 When R² is a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur suitable examples include morpholine, thiomorpholine, azetidine, imidazolidine, pyrrolidine, piperidine and piperazine.

When R² is a 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, examples include thienyl, furanyl, pyrrolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl, triazinyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, imidazolyl and tetrazolyl.

5

Preferably Ar is phenyl which can be optionally substituted by those substituent groups of the examples herein. Especially preferred substituents include one or more substituents, which can be the same or different, selected from hydroxymethyl, ethyl, [(2-hydroxypropyl)amino]methyl, [(2-hydroxy-1-methylethyl)amino]methyl, (1H-imidazol-1-ylmethyl), [(2,3-dihydroxypropyl)amino]methyl, 3-(morpholin-4-ylmethyl), {[2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl, {[1-benzyl-2-hydroxyethyl]amino}methyl, (3-hydroxypyrrolidin-1-yl)methyl, {[2-hydroxy-1-phenylethyl]amino}methyl, {[2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl, {[2-hydroxycyclohexyl]amino}methyl, {(2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl)amino}methyl, 3-hydroxypiperidin-1-ylmethyl, {[1-(hydroxymethyl)-2-methylpropyl]amino}methyl, {[4-(methylsulphonyl)benzyl]amino}methyl, and {[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino}methyl.

10
15

Substituents can be present on any suitable position of the Ar group. More than one substituent can be present, and these can be the same or different. One or two substituent groups are preferred.

20

Especially preferred compounds of the invention include those exemplified herein, both in free base form and as pharmaceutically acceptable salts.

25

Compounds of the invention can form pharmaceutically acceptable solvates and salts. The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, trifluoroacetic and methanesulphonic acids.

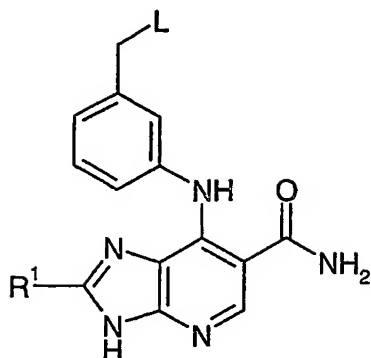
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The invention also provides a method of treating or preventing a disease mediated by JAK3 which comprises administering to a mammal a compound of formula (I) as defined above.

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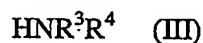
In a further aspect the invention provides a process for the preparation of a compound of formula (I) which comprises:

(a) for compounds of formula (I) where Y is NH and Ar is phenyl substituted by CH₂NR³R⁴, reaction of a compound of formula (II):



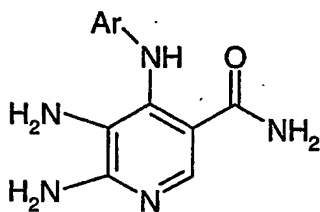
(II)

- 5 in which R^1 is as defined in formula (I) or is a protected derivative thereof and L is a leaving group, with a compound of formula (III):



- 10 in which R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof, or

(b) for compounds of formula (I) where Y is NH, reaction of a compound of formula (IV):



15

(IV)

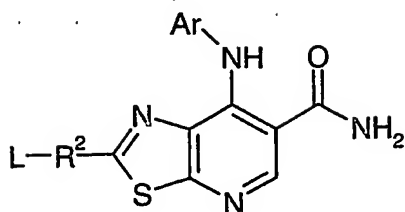
in which Ar is as defined in formula (I) or is a protected derivative thereof, with a compound of formula (V):

20



in which R^1 is as defined in formula (I) or is a protected derivative thereof, or

- 25 (c) for compounds of formula (I) where Y is S and R^1 is a group $-\text{R}^2\text{-(CH}_2\text{)}_p\text{-R}^3$ where R^2 is O or NH, reaction of a compound of formula (VI):



(VI)

- 5 in which Ar is as defined in formula (I) or is a protected derivative thereof, R^2 is O or NH, and L is a leaving group, with a compound of formula (VII) or (VIII):

 R^1 -OH (VII)10 R^1 -NH₂ (VIII)

in which R^1 is as defined in formula (I) or is a protected derivative thereof

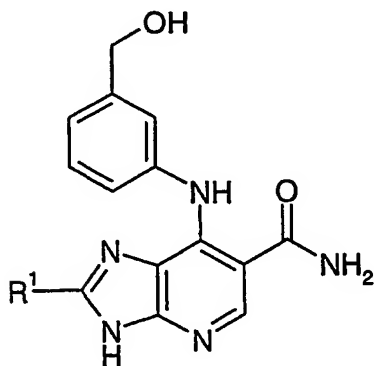
and optionally thereafter any of the above processes:

- 15
- removing any protecting groups
 - converting a compound of formula (I) into a further compound of formula (I)
 - forming a pharmaceutically acceptable salt.

20 Compounds of formula (I) can be converted into further compounds of formula (I) using standard chemistry.

Reaction of compounds (II) and (III) can be carried out in the presence of DIPA in a solvent such as NMP. Preferably the leaving group L is halogen, especially chloro. Compounds of formula (II) can be prepared by reacting compounds of formula (IX):

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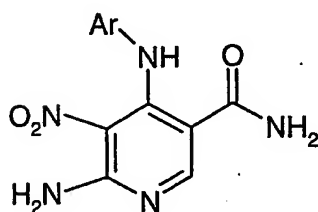
(IX)

in which R¹ is as defined in formula (II) with a chlorinating agent such as SOCl₂ in dichloromethane.

5

Reaction of compounds of formula (IV) and (V) can be carried out in a solvent such as DMF at elevated temperature, for example at about 120°C in the presence of an oxidant such as FeCl₃. Compounds of formula (IV) can be prepared from compounds of formula (X):

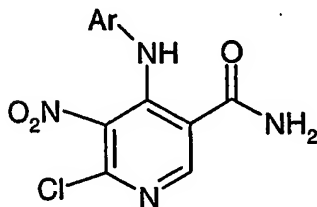
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(X)

15

in which Ar is as defined in formula (IV) by hydrogenation using a palladium catalyst in a protic solvent such as methanol. Compounds of formula (X) can be prepared from compounds of formula (XI):

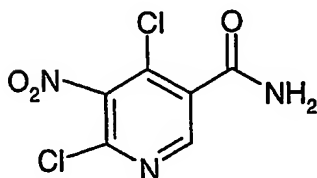


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(XI)

in which Ar is as defined in formula (IV) by treatment with ammonia. Compounds of formula (XI) can be prepared from compounds of formula (XII):

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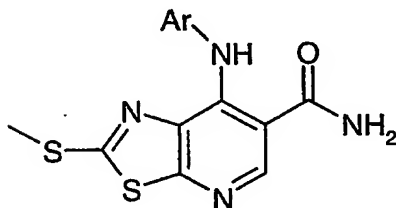


(XII)

by reaction with an amine Ar-NH_2 in which Ar is as defined in formula (IV) in an aprotic solvent such as DMF at elevated temperature.

Reaction of compounds (VI) with (VII) or (VIII) can be carried out in the presence of a suitable base at ambient or elevated temperatures. Suitable leaving groups for compounds (VI) include SO_2Me and SOMe .

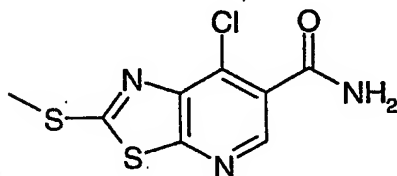
Compounds of formula (VI) can be prepared by oxidation of the corresponding sulphur compound (XIII):



(XIII)

using a reagent such as 3-chloroperbenzoic acid to give the sulfoxide or potassium permanganate to give the sulphone.

Compounds of formula (XIII) are prepared from compounds of formula (XIV):



(XIV)

by reacting with an amine Ar-NH_2 .

It will be appreciated that certain functional groups may need to be protected using standard protecting groups. The protection and deprotection of functional groups is for example, described in 'Protective Groups in Organic Chemistry', edited by J. W. F.

McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1999).

5 Diseases mediated by JAK3 include inflammatory, immunological, and bronchopulmonary disorders.

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, rhinitis, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia, and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

Preferably the compounds of the invention are used for the treatment of asthma, rheumatoid arthritis, and host versus graft rejection/transplantation.

20 The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cane, asthma, rhinitis, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia, and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, alone or in combination with a T-cell immunosuppresant or anti-inflammatory agents, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

30 The present invention also relates to a method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

35 In a still further aspect the invention provides the use of a compound of formula (IA) as a therapeutic agent.

The dose of the compound to be administered will depend on the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will preferably be in the range of from 0.1 mg/kg to 100 mg/kg.

- 5 The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols or dry powder formulations, e.g. formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration, e.g. in the form of sterile parenteral solutions or suspensions, or
10 by rectal administration, e.g. in the form of suppositories.

- The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are
15 compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

- Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably
20 finely divided. The finely divided compound preferably has a mass median diameter of less than 10 µm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C₈-C₂₀ fatty acid or salt thereof, (e.g. oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

- 25 The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

- 30 One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol, or an other polyol. Suitable carriers are sugars, e.g. lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each
35 containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit

meters the desired dose which is then inhaled by the patient. With this system the active compound, with or without a carrier substance, is delivered to the patient.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol; a starch, e.g. potato starch, corn starch or amylopectin; a cellulose derivative; a binder, e.g. gelatine or polyvinylpyrrolidone, and/or a lubricant, e.g. magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The term 'medical therapy' as used herein is intended to include prophylactic, diagnostic and therapeutic regimens carried out in vivo or ex vivo on humans or other mammals.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations, or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention further relates to combination therapies wherein a compound of the invention or a pharmaceutically acceptable salts or solvate thereof, or a pharmaceutical

composition or formulation comprising a compound of formula (1) is administered concurrently or sequentially with therapy and/or an agent for the treatment of any one of asthma, allergic rhinitis, cancer, COPD, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, osteoarthritis or osteoporosis.

5

In particular, for the treatment of the inflammatory diseases rheumatoid arthritis, psoriasis, inflammatory bowel disease, COPD, asthma and allergic rhinitis the compounds of the invention may be combined with agents such as TNF- α inhibitors such as anti-TNF monoclonal antibodies (such as Remicade, CDP-870 and D₂E₇ and TNF receptor immunoglobulin molecules (such as Enbrel®), non-selective COX-1 / COX-2 inhibitors (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib) low dose methotrexate, lefunomide, ciclesonide, hydroxychloroquine, d-penicillamine, auranofin or
15 parenteral or oral gold.

The present invention still further relates to the combination of a compound of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as zileuton, ABT-
20 761, fenleuton, tepoxalin, Abbott-79175, Abbott-85761, N-(5-substituted)-thiophene-2-alkylsulfonamides, 2,6-di-tert-butylphenol hydrazones, methoxytetrahydropyrans such as Zeneca ZD-2138, the compound SB-210661, pyridinyl-substituted 2-cyanonaphthalene compounds such as L-739,010, 2-cyanoquinoline compounds such as L-746,530, indole
25 and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to the combination of a compound of the invention together with a receptor antagonist for leukotrienes LTB₄, LTC₄, LTD₄, and LTE₄ selected from the group consisting of the phenothiazin-3-ones such as L-651,392, amidino compounds such as CGS-25019c, benzoxalamines such as ontazolast,
30 benzenecarboximidamides such as BIIL 284/260, and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

35 The present invention still further relates to the combination of a compound of the invention together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

The present invention still further relates to the combination of a compound of the invention together with a antihistaminic H₂ receptor antagonists such as cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

- 5 The present invention still further relates to the combination of a compound of the invention together with a gastroprotective H₂ receptor antagonist.

The present invention still further relates to the combination of a compound of the invention together with an α_1 - and α_2 -adrenoceptor agonist vasoconstrictor
10 sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

- 15 The present invention still further relates to the combination of a compound of the invention together with anticholinergic agents such as ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine, and telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a β_1 - to β_4 -adrenoceptor agonists such as metaproterenol,
20 isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol, or methylxanthanines including theophylline and aminophylline, sodium cromoglycate, or muscarinic receptor (M1, M2, and M3) antagonist.

- 25 The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the invention together with an inhaled glucocorticoid with reduced systemic side effects, such
30 as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate.

- The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the
35 stromelysins, the collagenases, and the gelatinases, as well as aggrecanase, especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-12.

The present invention still further relates to the combination of a compound of the invention together with other modulators of chemokine receptor function such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family), CXCR1, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

The present invention still further relates to the combination of a compound of the invention together with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antiseptis compounds such as Valant.

The present invention still further relates to the combination of a compound of the invention together with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

The present invention still further relates to the combination of a compound of the invention together with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The present invention still further relates to the combination of a compound of the invention together with (i) tryptase inhibitors, (ii) platelet activating factor (PAF) antagonists, (iii) interleukin converting enzyme (ICE) inhibitors, (iv) IMPDH inhibitors, (v) adhesion molecule inhibitors including VLA-4 antagonists, (vi) cathepsins, (vii) MAP kinase inhibitors, (viii) glucose-6 phosphate dehydrogenase inhibitors, (ix) kinin-B₁- and B₂-receptor antagonists, (x) anti-gout agents, e.g., colchicine, (xi) xanthine oxidase inhibitors, e.g., allopurinol, (xii) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone, (xiii) growth hormone secretagogues, (xiv) transforming growth factor (TGF β), (xv) platelet-derived growth factor (PDGF), (xvi) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF), (xvii) granulocyte macrophage colony stimulating factor (GM-CSF), (xviii) capsaicin cream, (xix) Tachykinin NK₁ and NK₃ receptor antagonists selected from the group consisting of NKP-608C, SB-233412 (talnetant), and D-4418, (xx) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892, (xxi) TNF α converting enzyme inhibitors (TACE), (xxii) induced nitric oxide synthase

inhibitors (iNOS) or (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (CRTH2 antagonists).

The compounds of the present invention may also be used in combination with
5 osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506, rapamycin, cyclosporine, azathioprine, and methotrexate.

The compounds of the invention may also be used in combination with existing therapeutic
10 agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2
15 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc and P2X7 receptor antagonists.

The compounds of the invention can also be used in combination with existing therapeutic
20 agents for the treatment of cancer. Suitable agents to be used in combination include:
(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas), antimetabolites (for example antifolates such as fluoropyrimidines like
25 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine and paclitaxel (Taxol®), antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin), antimetotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere), and
30 topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin),
(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and idoxifene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and
35 cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuporelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride,

- (iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function),
- (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erb2 antibody trastuzumab [Herceptin™] and the anti-erb3 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family,
- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin),
- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213,
- (vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense,
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy, and
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The following Examples illustrate the invention.

General methods All reactions were performed in dried glassware in an argon atmosphere at room temperature, unless otherwise noted. All solvents and reagents and solvents were used as received. Merck Silica gel 60 (0.040-0.063 mm) was used for preparative silica gel chromatography. A Kromasil KR-100-5-C18 column (250 x 20 mm, Akzo Nobel) and mixtures of acetonitrile/water at a flow rate of 10 ml/min was used for preparative HPLC. Reactions were monitored at 254 nm by analytical HPLC, using a Kromasil C-18 column (150 x 4.6 mm) and a gradient (containing 0.1% trifluoroacetic acid) of 5 to 100% of acetonitrile in water at a flow rate of 1 ml/min. Evaporations of solvents were performed under reduced pressure using a rotary evaporator at a maximum temperature of 40°C.

Products were dried under reduced pressure at 40 °C.

¹H-NMR spectra were recorded on a Varian Inova-400 or Unity-500+ instrument. The central solvent peak of chloroform-*d* (□_H 7.27 ppm), dimethylsulfoxide-*d*₆ (□_H 2.50 ppm) or methanol-*d*₄ (□_H 3.35 ppm) were used as internal references. Low resolution mass spectra obtained on a Hewlett Packard 1100 LC-MS system equipped with a APCI ionisation chamber.

Merck Silica gel 60 (0.040-0.063 mm) was used for preparative silica gel chromatography. A Kromasil KR-100-5-C18 column (250 x 20 mm, Akzo Nobel) and mixtures of acetonitrile/water at a flow rate of 10 ml/min was used for preparative HPLC. Reactions were monitored at 254 nm by analytical HPLC, using a Kromasil C-18 column (150 x 4.6 mm) and a gradient (containing 0.1% trifluoroacetic acid) of 5 to 100% of acetonitrile in water at a flow rate of 1 ml/min. Evaporations of solvents were performed under reduced pressure using a rotary evaporator at a maximum temperature of 40 °C. Products were dried under reduced pressure at 40 °C.

Thiazolopyridines

Example 1

7-[(2-Ethylphenyl)amino]-2-methoxy[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

1a) 7-Hydroxy-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxylic acid

The title compound was synthesized according to procedure described by D.C. Leysen; A. Haemers; W. Bollaert, *J. Heterocyclic Chem.* 1984, 21, 401.

1b) 7-Chloro-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

To a suspension of finely grinded 1a (3.70 g, 15.3 mmol) in thionyl chloride (100 mL) was added a drop of DMF. The suspension was stirred at 50 C for 4h. The thionyl chloride was

evaporated. Toluene was added. After a short time of stirring the toluene was evaporated. Acetone (125 mL) was added to the crude residue to form a suspension which was stirred and cooled to 0 °C. Cold Ammonium hydroxide (25%, 20 mL, 306 mmol) was added and the reaction was stirred for 1h and put in a refrigerator over night. The precipitate was
5 filtered off and washed twice with water and dried under vacuum at 70 °C over night.

Yield: 2.86g (72%).

¹H NMR (400 MHz, DMSO-d₆): δ 8.52 (s, 1H), 8.14 (s, 1H), 7.91 (s, 1H), 2.85 (s, 3H).

APCI-MS m/z: 259.9 [MH⁺].

10 **1c) 7-[(2-Ethylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide**

To a solution of **1b** (2.00 g, 7.7 mmol) and 2-ethylaniline (2.9 mL, 23.1 mmol) in DMSO (30 mL) was added BF₃·OEt₂ (0.95mL, 7.7 mmol). The solution was stirred over night at 110 °C. After cooling the reaction was poured into ice water and EtOAc. sodium carbonate
15 (5 %) was added to obtain an alkaline solution. The organic phase was separated and the water phase extracted twice with EtOAc. The combined organic phases were washed with three portions of water and brine. Dried over sodium sulphate and purified by flash chromatography (toluene:EtOAc 1:1).

Yield 1.98g, 5.75 mmol (75%).

20 ¹H NMR (400 MHz, DMSO-d₆) δ 10.99 (s, 1H), 8.67 (s, 1H), 8.31 (s, 1H), 7.70 (s, 1H), 7.27 - 7.25 (m, 1H), 7.16 - 7.13 (m, 2H), 7.09 - 7.07 (m, 1H), 2.58 (q, J = 7.5 Hz, 2H), 2.16 (s, 3H), 1.13 (t, J = 7.5 Hz, 3H).

APCI-MS m/z: 345.2 [MH⁺].

25

1d) 7-[(2-Ethylphenyl)amino]-2-(methylsulfinyl)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

A suspension of **1c** (1.00 g, 2.91 mmol) stirred in dichloromethane (15 mL) was cooled to -15 °C. 3-Chloroperbenzoic acid (680 mg, 3.05 mmol) was added portion wise. The
30 reaction was stirred 1h, allowed to reach room temperature and quenched with sodium thiosulfate (5 %). The organic phase was separated, washed with sodium bicarbonate and brine and dried over sodium sulphate. The product was purified by flash chromatography (EtOAc as eluent).

Yield: 910 mg, 2.52 mmol (87%).

35 ¹H NMR (400 MHz, DMSO-d₆) δ 11.28 (s, 1H), 8.84 (s, 1H), 8.40 (s, 1H), 7.78 (s, 1H), 7.27 - 7.26 (m, 1H), 7.20 - 7.15 (m, 1H), 7.14 - 7.10 (m, 2H), 2.70 (s, 3H), 2.57 (q, J = 7.4 Hz, 2H), 1.11 (t, J = 7.6 Hz, 3H).

APCI-MS M/Z: 361.1 [MH⁺].

1e) 7-[(2-Ethylphenyl)amino]-2-(methylsulfonyl)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide Compound **1d** (600 mg, 1.74 mmol) was dissolved in HOAc (16 mL). The solution was cooled in an ice bath. When the solution started to freeze a slow addition of potassium permanganate (560 mg, 3.52 mmol) dissolved in water (12 mL) was started. After 20 min the addition was completed. The stirring was continued for an additional 30 min. A saturated solution of sodium bisulphite (2.0 mL) was added. A precipitate was formed. The suspension was centrifuged and the supernatant was collected and extracted with chloroform. The organic layer was separated, washed twice with sodium bicarbonate (5%) and brine, and dried over sodium sulphate. The product was purified by flash-chromatography (toluene: EtOAc 4:6).
Yield: 101 mg (15%).
APCI-MS m/z: 377.2 [MH+].

1f) 7-[(2-Ethylphenyl)amino]-2-methoxy[1,3]thiazolo[5,4-b]pyridine-6-carboxamide **1e** (20 mg, 0.052 mmol) was placed in a dry reaction flask. Sodium methoxide (0.35M in methanol, 0.16 mL, 560 μ mol) was added. The reaction was stirred at room temperature for 2h and then quenched by adding water. The mixture was extracted with chloroform. The organic layer was separated and washed twice with water and dried over sodium sulphate. The product was purified by flash chromatography (toluene:EtOAc 1:1).
Yield: 10 mg (59%).
 ^1H NMR (400 MHz, DMSO- d_6) δ 10.79 (s, 1H), 8.62 (s, 1H), 8.28 (s, 1H), 7.67 (s, 1H), 7.23 (dd, J = 7.2, 1.9 Hz, 1H), 7.12 (qd, J = 7.3, 5.4 Hz, 2H), 7.02 (dd, J = 7.3, 1.7 Hz, 1H), 3.60 (s, 3H), 2.59 (q, J = 7.8 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).
APCI-MS m/z: 329.2 [MH+].

Example 2

7-[(2-methylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide trifluoroacetate

The title compound was prepared in an analogous way to **1c** (100 mg, 0.38 mmol), 2-methylaniline (0.123 mL, 1.15 mmol) and boron trifluoride ethyl etherate (0.047 mL, 0.38 mmol) in DMSO (2 mL). The product was purified by prep-HPLC.
Yield: 17 mg, 0.038 mmol (10%).
APCI-MS m/z: 331.2 [MH+]

Example 3

7-[(3-(hydroxymethyl)-2-methylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide trifluoroacetate

The title compound was prepared in an analogous way to **1c** (100 mg, 0.38 mmol), 3-(hydroxymethyl)-2-methylaniline (158 mg, 1.15 mmol) and boron trifluoride ethyl etherate (0.047 mL, 0.38 mmol) in dmso (2 mL). The product was purified by prep-HPLC. Yield: 53 mg, 0.11 mmol (29%).

5 APCI-MS m/z: 361.2 [MH+]

Example 4-7 were prepared in an analogous way to **1f**.

Example 4

10 2-[2-(Dimethylamino)ethoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

APCI-MS m/z: 386.2 [MH+].

Example 5

15 2-[3-(Dimethylamino)propoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

APCI-MS m/z: 400.2 [MH+].

Example 6

20 7-[(2-Ethylphenyl)amino]-2-(2-morpholin-4-ylethoxy)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

APCI-MS m/z: 428.2 [MH+].

Example 7

25 7-[(2-Ethylphenyl)amino]-2-[(3-morpholin-4-ylpropyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

APCI-MS m/z: 441.2 [MH+].

30 Example 8-10 were prepared in an analogous way to example **1f** using **1d** as reactant and at slightly elevated temperature (50°C).

Example 8

35 2-[4-(Aminocarbonyl)phenoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo [5,4b]pyridine-6-carboxamide

APCI-MS m/z: 434.1 [MH+].

Example 9

2-(3-aminophenoxy)-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide bis(trifluoroacetate)

APCI-MS m/z: 406.1 [MH⁺].

Example 10

7-[(2-ethylphenyl)amino]-2-(4-methoxyphenoxy)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide trifluoroacetate

APCI-MS m/z: 421.1 [MH⁺].

Imidazopyridines**Example 1**

7-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)

1a) Methyl 4,6-dichloro-5-nitronicotinate

The title compound was prepared according to the protocol of J. P. Sanchez and R. D. Gogliottias, *J. Heterocyclic Chem.* 1993, 30, 855-859.

1b) Methyl 6-chloro-4-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-5-nitronicotinate A solution of Methyl 4,6-dichloro-5-nitronicotinate (603 mg, 2.40 mmol), 2-Ethyl-3-hydroxymethyl-aniline (363 mg, 2.40 mmol, 1.0 equiv.) and ethyl(diisopropyl)amine (373 mg, 2.88 mmol, 1.2 equiv.) was stirred at 50°C over night. Addition of water, extraction with ethylacetate followed by washing with brine and drying over sodium sulfate resulted in a crude product. After chromatography on silica gel [methyl(*tert*-butyl)ether/heptane = 4:1] 466 mg of the title compound were obtained as a yellow solid. ¹H-NMR (400MHz, CDCl₃): δ 10.37 (s, 1H), 8.85 (s, 1H), 7.39 (d, *J* 7.1Hz, 1H), 7.14 (t, *J* 7.9Hz, 1H), 6.97 (d, *J* 7.7Hz, 1H), 4.76 (s, 2H), 4.00 (s, 3H), 2.75 (q, *J* 7.5Hz, 2H), 1.22 (t, *J* = 7.7Hz, 3H).

1c) 6-Amino-4-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-5-nitronicotinamide

The reaction was carried out in a sealed steel tube equipped with a glass inlet. Compound 1b (436 mg, 1.19 mmol) was placed in the reaction vessel and liquid ammonia was condensed in at -78°C. Then the mixture was allowed to warm up to room temperature. With a delay of 12 h the reaction mixture was warmed up to 80°C for additional 8 h. Then the reaction vessel was cooled down to -78°C, opened and ammonia was allowed to evaporate. Filtration of the crude on silica gel (EtOAc/Aceton = 9:1) afforded 239 mg (61%) of the pure title compound as a yellow solid.

¹H-NMR (400MHz, DMSO-d₆): δ 11.84 (s, 1H), 8.49 (s, 1H), 8.10 (s, 1H), 7.49 (s, 1H), 7.39 (s, 2H), 7.13 (d, *J* 7.0Hz, 1H), 6.98 (t, *J* 7.8Hz, 1H), 6.69 (d, *J* 7.3Hz, 1H), 5.14 (t, *J* 5.5Hz, 1H), 4.54 (d, *J* 5.5Hz, 2H), 2.64 (q, *J* 7.5Hz, 2H), 1.14 (t, *J* 7.3Hz, 3H).

1d) 5,6-Diamino-4-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]nicotinamide

Compound **1c** (2.22g, 6.71 mmol) was dissolved in methanol (40 ml) and palladium (10% on charcoal, 450 mg) was added. The mixture was stirred under normal pressure under a hydrogen atmosphere at room temperature over night. Filtration over celite and evaporation of the solvent resulted in the title compound as a colourless solid in quantitative yields.

¹H-NMR (400MHz, DMSO-d₆): δ 9.17 (s, 1H), 7.88 (s, 1H), 7.80 (s, 1H), 7.14 (s, 1H), 6.98 (t, *J* 7.7Hz, 1H), 6.92 (d, *J* 6.7Hz, 1H), 6.16 (d, *J* 7.4Hz, 1H), 5.90 (s, 2H), 5.03 (t, *J* 5.1Hz, 1H), 4.53 (d, *J* 4.9Hz, 2H), 3.72 (s, 2H), 2.72 (q, *J* = 7.5Hz, 2H), 1.21 (t, *J* 7.4Hz, 3H).

APCI-MS: *m/z* 302.2 [MH⁺].

1e) 7-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)

A solution of compound **1d** (18 mg, 59.0 μmol), benzaldehyde (7mg, 6.6 μL, 66.0 μmol, 1.1 equiv.) and a catalytic amount of *p*-toluenesulfonic acid monohydrate in DMF (400μL) was stirred at 120°C for 1h. After cooling down the mixture was diluted with acetonitrile (2.5 mL) and water (2mL) and subjected to a reversed phase HPLC. After freeze-drying 8 mg (27 %) of the title compound as its corresponding trifluoroacetate were obtained as a white powder. The NMR was recorded from the neutralized product.

¹H-NMR (400MHz, DMSO-d₆): δ 13.30 (s, 1H), 11.13 (s, 1H), 8.59 (s, 1H), 8.10 (s, 1H), 7.40 (m, 3H), 7.67 (m, 1H), 7.40 (m, 3H), 7.18 (m, 2H), 7.09 (t, *J* 7.4Hz, 1H), 5.10 (t, *J* 5.0Hz, 1H), 4.58 (d, *J* 4.7Hz), 2.72 (q, *J* 7.3Hz, 2H), 1.15 (t, *J* 7.2Hz, 3H).

APCI-MS: *m/z* 388.1 [MH⁺].

The title compounds of examples 2-26 were prepared according to the procedure described for example 1. In some cases FeCl₃ instead of *p*-toluenesulfonic acid was used to catalyze the reaction of step 1e.

7-[(2-ethylphenyl)amino]-2-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
2-[4-(dimethylamino)phenyl]-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroacetate)

7-[(2-ethylphenyl)amino]-2-(3-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)

- 7-[(2-ethylphenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 2-(3,4-dihydroxyphenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 5 2-(3-cyanophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 2-(4-cyanophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-[(2-ethylphenyl)amino]-2-(4-hydroxy-3-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 10 2-(3,4-difluorophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 2-(3-chloro-4-hydroxyphenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 15 7-[(2-ethylphenyl)amino]-2-(1H-imidazol-4-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroacetate)
- 7-[(2-ethylphenyl)amino]-2-[4-(methylsulfonyl)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 2-[4-(acetylamino)phenyl]-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 20 7-[(2-ethylphenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 7-[(2-ethylphenyl)amino]-2-{4-[(2-hydroxyethyl)(methyl)amino]phenyl}-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroacetate) (salt)
- 25 7-[(2-ethylphenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroacetate)
- 7-[(2-ethylphenyl)amino]-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 30 7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethylphenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 35 7-[(2-ethylphenyl)amino]-2-pyridin-3-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-[(2-ethylphenyl)amino]-2-pyridin-2-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate

- 2-[4-(2-[[tert-butyl(diphenyl)silyl]oxy]ethoxy)phenyl]-7-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
5 7-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

Example 27

- 7-[(2-ethyl-3-[(2-hydroxypropyl)amino]methyl)phenyl]amino]-2-(4-methoxyphenyl)-
10 3H-imidazo[4,5-b]pyridine-6-carboxamide

Treatment of a suspension of example 26 in dichloromethane with thionyl chloride at room temperature generated the corresponding chloride. The volatiles were removed in vacuo, and the residue was dissolved in NMP. The chloride (0.1M) was then treated with 1.5 eq of
15 1-amino-propan-2-ol (0.2M in NMP) and 3eq of DIPEA(0.2M in NMP) and heated at 120 °C for 12h generating the title compound in good yield.

The title compounds of examples 28-93 were prepared in analogous manner to example 26:

20

Examples 28 - 93

- 7-[(2-ethyl-3-[(2-hydroxypropyl)amino]methyl)phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-[(2-hydroxypropyl)amino]methyl)phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
25 7-[(2-ethyl-3-[(2-hydroxy-1-methylethyl)amino]methyl)phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[[2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
30 7-[(3-[(2,3-dihydroxypropyl)amino]methyl)-2-ethylphenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[[2-ethyl-3-(morpholin-4-ylmethyl)phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
35 7-[[3-([[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino)methyl]-2-ethylphenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-([3-([[(1S)-1-benzyl-2-hydroxyethyl]amino)methyl]-2-ethylphenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-([4-(2-hydroxyethyl)piperazin-1-yl)methyl]phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 5 7-([2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-([2-ethyl-3-([[(1S)-2-hydroxy-1-phenylethyl]amino)methyl]phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-[(2-ethyl-3-([(2R)-2-(hydroxymethyl)pyrrolidin-1-yl)methyl]phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-([2-ethyl-3-([[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 7-[(2-ethyl-3-([(2-hydroxycyclohexyl)amino)methyl]phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-([2-ethyl-3-([[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino)methyl]phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-([2-ethyl-3-([[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-([2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-([2-ethyl-3-([1-(hydroxymethyl)-2-methylpropyl]amino)methyl]phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-([2-ethyl-3-([4-(methylsulfonyl)benzyl]amino)methyl]phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-([3-([2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino)methyl]-2-ethylphenyl)amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-[(2-ethyl-3-([(2-hydroxypropyl)amino)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 35 7-[(2-ethyl-3-([(2-hydroxy-1-methylethyl]amino)methyl]phenyl)amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-([2-ethyl-3-(1H-imidazol-1-yl)methyl]phenyl)amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
7-([3-([2-(2,3-dihydroxypropyl)amino)methyl]-2-ethylphenyl)amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-{{2-ethyl-3-(morpholin-4-ylmethyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-{{3-({[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl)-2-ethylphenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 5 7-{{3-({[(1S)-1-benzyl-2-hydroxyethyl]amino}methyl)-2-ethylphenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-{{4-(2-hydroxyethyl)piperazin-1-yl}methyl}phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-{{3-hydroxypyrrolidin-1-yl}methyl}phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-{{2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-{{(2R)-2-(hydroxymethyl)pyrrolidin-1-yl}methyl}phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 7-{{2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-{{(2-hydroxycyclohexyl)amino}methyl}phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-{{2-ethyl-3-({[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-({[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-{{2-ethyl-3-{{3-hydroxypiperidin-1-yl}methyl}phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-({[1-(hydroxymethyl)-2-methylpropyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-{{2-ethyl-3-({[4-(methylsulfonyl)benzyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-{{2-ethyl-3-{{(2-hydroxypropyl)amino}methyl}phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 35 7-{{2-ethyl-3-{{(2-hydroxy-1-methylethyl)amino}methyl}phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate

- 7-[(3-[(2,3-dihydroxypropyl)amino]methyl)-2-ethylphenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-(morpholin-4-ylmethyl)phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 5 7-[(3-[(1S)-1-benzyl-2-hydroxyethyl]amino)methyl]-2-ethylphenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-[(2-ethyl-3-[(1S)-2-hydroxy-1-phenylethyl]amino)methyl]phenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl)methyl]phenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 7-[(2-ethyl-3-[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(2-hydroxycyclohexyl)amino]methyl]phenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-[(2-ethyl-3-[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino)methyl]phenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-[(2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(2-hydroxypropyl)amino]methyl]phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-[(2-ethyl-3-[(2-hydroxy-1-methylethyl)amino]methyl]phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-(1H-imidazol-1-yl)methyl]phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 35 7-[(3-[(2,3-dihydroxypropyl)amino]methyl)-2-ethylphenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-(morpholin-4-ylmethyl)phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate

7-({3-({[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl)-2-ethylphenyl]amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
 7-[(2-ethyl-3-{{4-(2-hydroxyethyl)piperazin-1-yl}methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
 5 7-({2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
 7-({2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl}amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
 7-[(2-ethyl-3-{{(2R)-2-(hydroxymethyl)pyrrolidin-1-yl}methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
 10 7-({2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
 7-[(2-ethyl-3-{{(2-hydroxycyclohexyl)amino}methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
 15 7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl}amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

Pharmacological Data

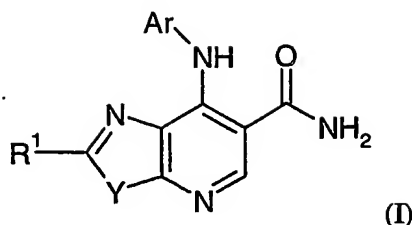
20 JAK3 HTRF assay

The JAK3 kinase assay utilizes a fusion protein (Jak3 kinase domain fused to Glutathione S-transferase, GST) coexpressed in E.Coli with GroEL/S, and purified by affinity chromatography on Glutathione Sepharose. The enzyme is diluted in 10 mM Tris-HCl,
 25 150 mM NaCl, 5% mannitol, 2 mM 2-mercaptoethanol and 30% glycerol. The substrate in the kinase reaction is a biotinylated peptide of the autophosphorylation site of JAK3 (biotin-LPDKDYYVVREPG) used at 2 μ M. Assay conditions are as follows: JAK3, compound and substrate are incubated in 25 mM Trizma base, 5 mM MgCl₂, 5 mM MnCl₂, 0.05% TritonX-100 and 2 μ M ATP for 45 min at RT. Reaction volume is 20 μ M.
 30 Stopsolution is added for a final concentration of 100 μ M EDTA. Finally 0.065 mg/ml PT66-K and 10.42 μ M SA-XL665 are added in 50 mM Hepes, 0.5 M KF and 0.1% BSA. The plate is read in a Discovery instrument after 60 min incubation.

The compounds of the examples have an IC₅₀ less than 25 μ M

CLAIMS

1. A compound of formula (I):



wherein:

Y is NH, S or O;

R¹ is phenyl or a 5- to 7-membered heteroaromatic ring containing 1 to 3 heteroatoms, each of which is optionally substituted by one or more groups selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, S(O)_nC₁-C₈ alkyl or a group -R²-(CH₂)_p-R³;

n is 0, 1 or 2;

R² is a bond, NH, NC₁-C₈ alkyl, S or O;

p is 0 - 3;

R³ is NR⁴R⁵ where R⁴ and R⁵ are independently hydrogen or C₁-C₈ alkyl, or R³ is a phenyl ring, a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, or a 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, each of which can optionally substituted by one or more groups selected from CONR⁴R⁵, NR⁴R⁵, C₁-C₈ alkyl, C₁-C₈ alkoxy, S(O)_nC₁-C₈ alkyl, hydroxyl, CN, halogen, NHCOC₁-C₈alkyl, R²-(CH₂)_p-OH or morpholine;

n is 1 to 4;

Ar is phenyl which can be optionally substituted by one or more groups selected from halogen, hydroxy, cyano, C₁-C₈ alkyl (itself optionally substituted by one or more hydroxy or cyano groups or fluorine atoms), CH₂-R⁶; CH₂O(CH₂)_nOC₁₋₆ alkyl, C₁-C₈ alkyl-NR³-R⁴, or a C₂₋₆ alkyl chain optionally containing an NR⁷ group in the chain and optionally

substituted by one or more OH groups and optionally terminating in a cycloalkyl or phenyl group, the cycloalkyl and phenyl groups themselves being optionally substituted by one or more hydroxyl groups;

- 5 R^6 is a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, an aryl or 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, each of which can optionally substituted by one or more substituents selected from hydroxyl or hydroxymethyl;

- 10 R^7 is hydrogen or C_{1-6} alkyl;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 in which NH or S.

15

3. A compound according to claim 1 or 2 in which R^1 is pyridyl or phenyl optionally substituted by SCH_3 , $SOCH_3$, $O-Ph-CONH_2$, $NH(CH_2)_3$ -morpholine, $O(CH_2)_3-N(CH_3)_2$, $O(CH_2)_2$ -morpholine, OCH_3 , $O(CH_2)_2-N(CH_3)_2$, 2-(3-aminophenoxy), 4-methoxyphenoxy, OH, $N(CH_3)_2$, OCH_3 , CN, fluoro, chloro, $S(O)_2CH_3$, $NHCOCH_3$,
20 $O(CH_2)_2OH$, $N(CH_3)(CH_2)_2OH$, morpholine or $O(CH_2)_2-OH$

20

4. A compound according to claim 1 or 2 in which the Ar is substituted by selected from hydroxymethyl, ethyl, [(2-hydroxypropyl)amino]methyl, [(2-hydroxy-1-methylethyl)amino]methyl, (1H-imidazol-1-yl)methyl, [(2,3-dihydroxypropyl)amino]methyl, 3-(morpholin-4-yl)methyl, {[2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl, {[1-benzyl-2-hydroxyethyl]amino}methyl, (3-hydroxypyrrolidin-1-yl)methyl, {[2-hydroxy-1-phenylethyl]amino}methyl, {(2-hydroxy-1-(hydroxymethyl)-2-phenylethyl)amino}methyl, {(2-hydroxycyclohexyl)amino}methyl, {(2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl)amino}methyl, 3-hydroxypiperidin-1-ylmethyl, {[1-(hydroxymethyl)-2-methylpropyl]amino}methyl, {[4-(methylsulphonyl)benzyl]amino}methyl, or {[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino}methyl.

30

- 35 5. A compound according to claim 1 which is:
7-[[3-(hydroxymethyl)-2-methylphenyl]amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide
7-[(2-ethylphenyl)amino]-2-(methylsulfinyl)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

- 2-[4-(aminocarbonyl)phenoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide
7-[(2-ethylphenyl)amino]-2-[(3-morpholin-4-ylpropyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide
5 2-[3-(dimethylamino)propoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide
7-[(2-ethylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide
7-[(2-ethylphenyl)amino]-2-(2-morpholin-4-ylethoxy)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide
10 7-[(2-ethylphenyl)amino]-2-methoxy[1,3]thiazolo[5,4-b]pyridine-6-carboxamide
7-[(2-methylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide
2-[2-(dimethylamino)ethoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide
2-(3-aminophenoxy)-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide
15 bis(trifluoroacetate)
7-[(2-ethylphenyl)amino]-2-(4-methoxyphenoxy)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide
7-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide
20 7-[(2-ethylphenyl)amino]-2-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
2-[4-(dimethylamino)phenyl]-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroa
7-[(2-ethylphenyl)amino]-2-(3-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethylphenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-
25 carboxamide 2-(3,4-dihydroxyphenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide
2-(3-cyanophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide
2-(4-cyanophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethylphenyl)amino]-2-(4-hydroxy-3-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-
30 carboxamide
2-(3,4-difluorophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide
2-(3-chloro-4-hydroxyphenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide
35 7-[(2-ethylphenyl)amino]-2-(1H-imidazol-4-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethylphenyl)amino]-2-[4-(methylsulfonyl)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
2-[4-(acetylamino)phenyl]-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-[(2-ethylphenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethylphenyl)amino]-2-{4-[(2-hydroxyethyl)(methyl)amino]phenyl}-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 5 7-[(2-ethylphenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethylphenyl)amino]-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethylphenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethylphenyl)amino]-2-pyridin-3-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide 7-[(2-ethylphenyl)amino]-2-pyridin-2-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 2-[4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)phenyl]-7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-[(2-ethyl-3-{[(2-hydroxypropyl)amino]methyl}phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-{[(2-hydroxypropyl)amino]methyl}phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-[(2-ethyl-3-{[(2-hydroxy-1-methylethyl)amino]methyl}phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{[2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl]amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(3-{[(2,3-dihydroxypropyl)amino]methyl}-2-ethylphenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-{[2-ethyl-3-(morpholin-4-ylmethyl)phenyl]amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{[3-{[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl]-2-ethylphenyl]amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 35 7-{[3-{[(1S)-1-benzyl-2-hydroxyethyl]amino}methyl]-2-ethylphenyl]amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-({2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 5 7-[(2-ethyl-3-({[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-[(2-ethyl-3-({[(2-hydroxycyclohexyl)amino]methyl}phenyl)amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-({[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl)phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 7-({2-ethyl-3-({[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-({2-ethyl-3-({[1-(hydroxymethyl)-2-methylpropyl]amino}methyl)phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-({[4-(methylsulfonyl)benzyl]amino}methyl)phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({3-({[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino}methyl)-2-ethylphenyl}amino)-2-[4-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-[(2-ethyl-3-({[(2-hydroxypropyl)amino]methyl}phenyl)amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-({[(2-hydroxy-1-methylethyl)amino]methyl}phenyl)amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-({2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl}amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({3-({[(2,3-dihydroxypropyl)amino]methyl}-2-ethylphenyl)amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-(morpholin-4-ylmethyl)phenyl}amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 35 7-({3-({[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl)-2-ethylphenyl}amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({3-({[(1S)-1-benzyl-2-hydroxyethyl]amino}methyl)-2-ethylphenyl}amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-[(2-ethyl-3-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide 7-[(2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 5 7-[(2-ethyl-3-([(1S)-2-hydroxy-1-phenylethyl]amino)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-([(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-[(2-ethyl-3-[(2-hydroxycyclohexyl)amino]methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-([(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 7-[(2-ethyl-3-([(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-[(2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-([1-(hydroxymethyl)-2-methylpropyl]amino)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-([4-(methylsulfonyl)benzyl]amino)methyl]phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-[(2-ethyl-3-[(2-hydroxypropyl)amino]methyl]phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-[(2-hydroxy-1-methylethyl)amino]methyl]phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-[(2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(3-([(2,3-dihydroxypropyl)amino]methyl)-2-ethylphenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-(morpholin-4-ylmethyl)phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 35 7-[(3-([(1S)-1-benzyl-2-hydroxyethyl]amino)methyl)-2-ethylphenyl]amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
7-[(2-ethyl-3-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-({2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-([2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl]amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 5 7-[(2-ethyl-3-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]phenylamino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-([2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl]amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-[(2-ethyl-3-[(2-hydroxycyclohexyl)amino]methyl]phenylamino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-([2-ethyl-3-({[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl)phenyl]amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 7-([2-ethyl-3-({[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl]amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide)
- 7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl}amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-[(2-ethyl-3-[(2-hydroxypropyl)amino]methyl]phenylamino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(2-hydroxy-1-methylethyl)amino]methyl]phenylamino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-([2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-[(3-[(2,3-dihydroxypropyl)amino]methyl)-2-ethylphenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-([2-ethyl-3-(morpholin-4-ylmethyl)phenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-([3-({[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl)-2-ethylphenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 35 7-([2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]phenylamino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-([2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide)

7-[(2-ethyl-3-[(2-hydroxycyclohexyl)amino]methyl)phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-([2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-([2-ethyl-3-({[1-(hydroxymethyl)-2-methylpropyl]amino}methyl)phenyl]amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

or a pharmaceutically acceptable salt thereof.

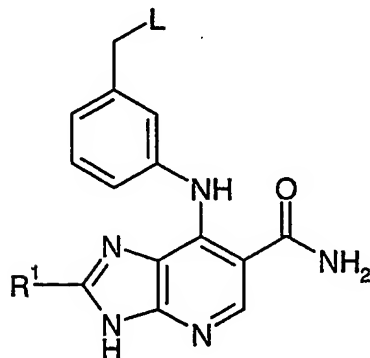
6. A compound of formula (I) as defined in any one of claims 1 to 5 for use in therapy

7. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

8. A method of treating a disease or condition mediated by JAK3 which comprises administering to a patient in need of such treatment a compound of formula (I) as defined in claims 1 to 5 or a pharmaceutically acceptable salt thereof.

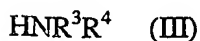
9. A method according to claim 8 in which the disease or condition is asthma, host versus graft rejection/transplantation or rheumatoid arthritis.

10. A process for the preparation of a compound of formula (I) which comprises:
(a) for compounds of formula (I) where Y is NH and Ar is phenyl substituted by $\text{CH}_2\text{NR}^3\text{R}^4$, reaction of a compound of formula (II):



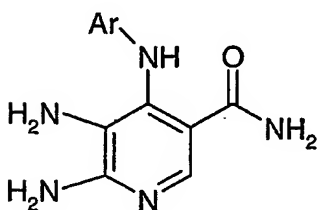
(II)

in which R^1 is as defined in formula (I) or is a protected derivative thereof and L is a leaving group, with a compound of formula (III):



in which R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof, or

(b) for compounds of formula (I) where Y is NH, reaction of a compound of formula (IV):



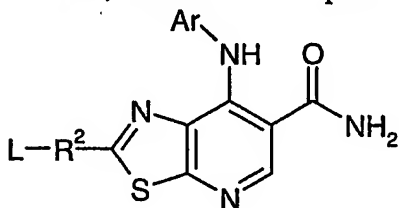
(IV)

in which Ar is as defined in formula (I) or is a protected derivative thereof, with a compound of formula (V):



in which R^1 is as defined in formula (I) or is a protected derivative thereof, or

(c) for compounds of formula (I) where Y is S and R^1 is a group $-R^2-(CH_2)_p-R^3$ where R^2 is O or NH, reaction of a compound of formula (VI):



(VI)

in which Ar is as defined in formula (I) or is a protected derivative thereof, R^2 is O or NH, and L is a leaving group, with a compound of formula (VII) or (VIII):



R^1-NH_2 (VIII)

in which R^1 is as defined in formula (I) or is a protected derivative thereof

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and optionally thereafter any of the above processes:

- removing any protecting groups
- converting a compound of formula (I) into a further compound of formula (I)
- forming a pharmaceutically acceptable salt.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/000694

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 471/04, C07D 513/04, C07D 498/04, A61K 31/437, A61P 11/06, A61P 37/00, A61P 19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN-CAPLUS, MEDLINE, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3996233 A (THEODOR DENZEL ET AL), 7 December 1976 (07.12.1976), column 6, line 39 - line 55 --	1-10
X	US 3953461 A (THEODOR DENZEL ET AL), 27 April 1976 (27.04.1976), column 4, line 3 - line 18 --	1-10
A	Vittori, Sauro et al, "N-Cycloalkyl Derivatives of Adenosine and 1-Deazaadenosine as Agonists and Partial Agonists of the A1 Adenosine Receptor", J. Med. Chem., Vol. 43, 2000, page 250 - page 260, tables 3,5 --	1-10

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 Sept 2004

Date of mailing of the international search report

13 -09- 2004

Name and mailing address of the ISA/

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Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/000694

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Vittori, Sauro et al, "Deaza- and Deoxyadenosine Derivatives: Synthesis and Inhibition of Animal Viruses as Human Infection Models", Nucleotides, Nucleotides & Nucleic Acids, vol. 22, no. 5-8, 2003, page 877 - page 881, compounds 15-20 --	1-10
A	Cristalli, Gloria et al, "Adenosine Deaminase Inhibitors: Structure-Activity Relationships in 1-Deazaadenosine and Erythro-9-(2-Hydroxy-3-Nonyl)Adenine Analogues", Drug Development Research, vol. 28, 1993, page 253 - page 258, figures 1-3 -- -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/2004

International application No.

PCT/SE 2004/000694

US	3996233	A	07/12/1976	CA	1054600	A	15/05/1979
				DE	2604748	A	19/08/1976
				FR	2299867	A,B	03/09/1976
				GB	1541692	A	07/03/1979
				JP	51105092	A	17/09/1976

US	3953461	A	27/04/1976	CA	1077484	A	13/05/1980
				DE	2609009	A	16/09/1976
				FR	2302738	A,B	01/10/1976
				GB	1539914	A	07/02/1979
				JP	51113894	A	07/10/1976

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2004/000694**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-9
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2004/000694

Claims 8-9 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.